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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/376,395	08/18/1999	LEAF HUANG	226272002201	6461

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/11/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/376,395	Applicant(s) HUANG ET AL.	
	Examiner Richard Schnizer	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-54,56-71,73-86,88-101,103-123 and 125-136* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-54,56-71,73-86,88-101,103-123 and 125-136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received and entered as Paper No. 13 on 9/24/01. Claims 55, 72, 87, 102, and 124 were canceled as requested. Claims 46-54, 56-71, 73-86, 88-101, 103-123, and 125-136 remain pending and are under consideration in this Office Action.

Rejections Withdrawn

The rejection of claims 113 and 115-136 under 35 USC 112, first paragraph for lack of written description is withdrawn in view of Applicant's argument.

The rejection of claims 49, 52-54, 57-59, 68, 70, 71, 73, 76, 80-86, 89-91, 100, 101, 106, 110-112, 118-123, and 126-128 is withdrawn in view of Applicant's amendments and arguments.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 113, 115, 116, 118-120, and 122-135 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 and 35-44 of U.S. Patent No. 6,008,202 ('202) for the reasons of record in Paper No. 11. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The invention claimed in 202' is a method of delivering to a cell in a human a drug/lipid/polycationic salt complex. See claims 1, 35, and 37. The complex may be formulated such that it has a positive charge excess of lipid and polycationic polypeptide to drug, and the drug may be a nucleic acid. See claims 2 and 8. Claims 113, 115, 116, 118-120, and 122-135 of the instant application are drawn to the same method and same compositions, except that they recite limitations concerning the route of administration of the complex, including intraperitoneal administration. Specific routes of administration are not claimed in '202'. However, '202' broadly claims methods of delivering the claimed complexes, and discloses, a working example of intraperitoneal administration of a cationic complex. For these reasons, intraperitoneal delivery of the instantly claimed compositions is obvious.

Applicant has not responded to this rejection with any argument, indicating instead that a terminal disclaimer will be filed upon receipt of a notice of allowance. For this reason the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-136 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising the E1A gene, at least one lipid species, and a polycationic polypeptide salt, wherein the composition has a net positive charge, and for a method of administering the composition to an animal wherein the composition is delivered directly to the site of tumor cells intended to receive the E1A gene, as taught in US Patent 6,008,202, does not reasonably provide enablement for a composition, or a method of administering the composition, wherein the composition comprises a net neutral or net negative charge, or wherein the composition has a net positive charge but does not comprise a gene encoding EIA, or for any claimed composition comprising an asialoglycoprotein targeting ligand, or for methods of systemic administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons of record in Paper no. 11.

The claimed invention encompasses compositions comprising a nucleic acid, at least one lipid species, and a polycationic polypeptide salt, and methods of making and using the compositions. Claims 46-76, 79, 83, and 117 require that the composition must have a net

negative or neutral charge. Claims 77-112 require the use of a targeting ligand. In Paper No. 10, Applicant elected asialoglycoprotein as the targeting ligand under consideration. Claims 113-136 encompass various routes of administration. The elected invention requires that the nucleic acid is intended to be used as a drug. The specification defines the term "drug" at page 4, lines 15-18 as a molecular entity administered to an individual for the purpose of therapy. For this reason, a "drug" as defined by the specification must be therapeutic if it is to be used as intended. Therefore, in order to enable the invention commensurate in scope with the claims, the specification must teach how to use the claimed compositions as drugs, i.e. therapeutically.

Response to Arguments

Applicant's arguments filed 9/24/01 have been fully considered but they are not persuasive.

Applicant argues at page 11 of the response that the specification teaches how to make and use the claimed compositions and methods, pointing to several passages in the specification which provide details on the nature of the charge of the composition, the nature of the nucleic acid, the nature of targeting ligands, and routes of administration. See page 5, lines 10-13, page 17, lines 16-25; page 24, lines 5-8; page 15, line 5; page 21, lines 1-9 and 21-27; and page 27, lines 24-26. Applicant argues at page 12 of the response that the specification teaches uses for the claimed invention other than gene therapy. Specifically Applicant asserts that the invention relates to vehicles for the transfer of nucleic acids into cells, and is not solely directed to gene

therapy. Applicant notes that the specification describes the transfection of cells with reporter genes.

These arguments are unpersuasive because the elected invention is drawn to drugs and methods of using drugs, wherein the drug is a nucleic acid. See for example original claim 46, and the restriction requirement of Paper No. 7. As noted above, the specification defines the term "drug" at page 4, lines 15-18 as a molecular entity administered to an individual for the purpose of therapy. Applicant has not provided any evidence or argument which would support the use of reporter genes as therapeutics.

At page 12 of the response, Applicant questions the appropriateness of considering enablement of the claimed compositions and methods within the context of gene therapy, noting that rejected claims are directed to complexes and methods of making the complexes. In response, the PTO asserts that the complexes must be viewed as drugs for the reasons given above and in Paper No. 11, and that Applicant has provide no reasoning or argument to support the position that the specification teaches how to use the claimed composition, commensurate in scope with the claims in light of the specification, as a drug *i.e.* for therapy.

Applicant argues at page 12 of the response that there is no legal requirement that the claims must be supported by a working example. This is true, however in view of the state of the art, and the unpredictability of gene therapy and vector targeting, as established in Paper No. 11; and in view of the breadth of the claims which encompass drugs and methods for the treatment of any disease; and in view of the lack of any teachings as to how to overcome the art-recognized

barriers to general gene therapy and targeted therapeutic delivery of nucleic acids; one of skill in the art could not use the invention commensurate in scope with the claims without the benefit of a working example.

Applicant argues at page 13 of the response that claims 77, 98, and 104, should be enabled because they differ from issued claims 8, 31, and 35 of US Patent 6,008,202 only by the addition of a targeting factor. Applicant is reminded that each application is considered on its own merits, and that enablement of a broad claim does not necessarily imply enablement of all of the encompassed embodiments. In this case, the elected targeting ligand is asialoglycoprotein. The specification has failed to teach how to use compositions comprising asialoglycoprotein as intended by the specification, *i.e.* for ligand-mediated delivery, for the reasons given at pages 8-10 of Paper No. 11, which were supported by the teachings of Perales (1994a), Perales (1994b), and Schlepper-Schaefer (1986). Applicant asserts that the Examiner has not provided support for the position that the teachings of Perales (1994a), Perales (1994b), and Schlepper-Schaefer (1986) would be applicable to the instant invention. This is unpersuasive because Applicant has provided no reason or argument indicating that these teachings should not apply. The cited art was relied upon to show that receptor-mediated gene targeting was unpredictable, particularly because the size of the ligand-bound delivery complex can influence the success of uptake. Specifically, Schlepper-Schaefer teaches that the asialoglycoprotein receptor cannot mediate uptake of particles greater than 7.8 nm in diameter. As noted in Paper No. 11, the specification fails to teach how to make particles of this size, and in fact teaches away from their use at page

11, lines 1 and 2. Applicant has failed to provide any evidence or argument indicating that the nature of the claimed complexes would somehow overcome the art-recognized limitation on the size of particles which can be targeted using asialoglycoprotein. Furthermore, because the specification has failed to teach how to make particles of the appropriate size, it fails to teach critical elements of the invention, so the Examiner's application of Genentech Inc. V. Novo Nordisk A/S at pages 10 and 11 of Paper No. 11 is proper.

Finally, Applicant argues at pages 13 and 14 of the response that the specification provides an enabling disclosure because it teaches that complexes may be delivered systemically by a variety of modes and routes of administration. This is unpersuasive because the PTO established in the paragraph bridging pages 7 and 8 of Paper No. 11 that systemic delivery of gene therapeutics is extremely unpredictable and could not be practiced with routine success by those of skill in the art at the time of the invention due in part to the difficulty in achieving vector targeting. Applicant has failed to provide any reasoning or evidence that the instant specification provides any teaching or examples that improve on the state of the art of systemic delivery of gene therapeutics. Inclusion of a targeting ligand in the composition does not enable systemic delivery for the reasons given at pages 7 and 8 of Paper No. 11 and supported therein by Miller (1995), Deonarain (1998) Verma (1997), Crystal (1995). Furthermore, inclusion of the elected asialoglycoprotein targeting ligand does not enable systemic delivery for the reasons given in the previous paragraph.

For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER